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| EXAMINER | |
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| BRISTOL, LYNN ANNE | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/560,098 | MIYAZAKI ET AL. | |
| | Examiner | Art Unit | |
| | LYNN BRISTOL | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,6,8 and 13-28* is/are pending in the application.

4a) Of the above claim(s) *13-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8 and 22-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/10/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/10/09 has been entered.

2. Claims 1, 6, 8, 13-28 are all the pending claims for this application.

3. Claims 3, 4, and 9-12 were cancelled and Claims 1, 6, and 8 were amended in the Response to the 6/10/09.

4. Claims 13-21 are withdrawn from examination.

5. Claims 1, 6, 8, and 22-28 are all the pending claims under examination.

6. Applicants amendments to the claims have necessitated new grounds for rejection.

### *Information Disclosure Statement*

7. The IDS of 6/10/09 has been considered and entered. The initialed and signed 1449 form of 6/10/09 is attached.

## ***Rejections Maintained***

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. The rejection of Claims 1, 6, 8 and 22 (and new Claims 23-28) under 35 U.S.C. 103(a) as being unpatentable over Ridgeway et al., (Protein Eng. 9:617-612 (1996); cited in the IDS of 4/28/06) in view of Peipp et al., (Biochem. Soc. Trans. 30:507-511 (2002); cited in the IDS of 4/28/06) and Shalaby et al., (J. Exp. Med. 175:217-225 (1992); cited in the IDS of 4/28/06) is maintained.

The rejection was set forth in the Office Action of 10/23/07 as follows:

"Ridgeway describes a process for producing a bispecific antibody having an Fc region, wherein the H chain and L chain which constitute a first set have a antigen recognition site and the H chain and L chain which constitute a second pair have another antigen recognition site and are expressed simultaneously, and the formation of the first pair and the second pair and the bonding of said first pair and second pair by knobs-in-hole are carried out simultaneously. Ridgeway also describe antibodies produced having antigen recognition sites comprising the H chain which makes up the first pair and the L chain which makes up the second pair. Ridgeway does not disclose expressing the first and second antibodies at different times but Peipp and Shalaby rectify this deficiency.

Peipp and Shalaby are discussed supra.

One skilled in the art would have been motivated at the time of the invention to have made the process for producing a bispecific antibody having an Fc region and been reasonably assured of success based on the disclosures of Ridgeway, Peipp and Shalaby. The method of Ridgeway could readily have been modified by one of skill in the art based on Pipp and Shalaby disclosing that the separate expression of an H chain and L chain which constitute a first pair having a particular antigen recognition site and an H chain and L chain which constitute a second pair having another antigen recognition site, and to bond their respective H chain and L chains in advance, forming a first pair and a second pair having antigen recognition site, and subsequently bonding the first pair and second pair via knob-in-hole, in order to prevent the production of antibodies having antigen recognition sites comprising undesirable sets and to efficiently produce the target bispecific antibody. Further one of skill in the art could introduce an optimum expression regulating factor and carry out the expression of the H chain and L chain which constitute the first pair, and an H chain and L chain which constitute the second pair in separate cells at different times. Because Ridgeway taught the general method for producing bispecific antibodies and Peipp and Shalaby describe different techniques for expressing different antibody pairs from different vectors could be

accomplished in E. coli, one of ordinary skill in the art could have readily introduced the vector system of Peipp or Shalaby into the method of Ridgeway and would be reasonably assured that the expressed antibody pairs would have formed a bispecific antibody."

The rejection was maintained in the Office Action of 9/11/08 as follows:

"Applicants' allegations on p. 11 of the Response of 4/23/08 have been considered but are not found persuasive. Applicants allege "Indeed, the knobs-in-holes method used by Ridgeway is very similar to that of Carter"; and the rejection over Ridgeway, Peipp and Shalaby is incorrect for the same reasons the rejection over Carter, Peipp and Shalaby is incorrect.

Response to Arguments

Applicants do not appear to have taken the time to review Ridgeway, or the disclosure relied on by the examiner was overlooked. Ridgeway teaches co-transfection of phagemids encoding the anti-CDR3 L chain and **H** chain into human embryonic kidney cells, 293S, *together* with a CD4IgG variant encoding phagemid. This is interpreted as the antibody being expressed by the same cell. Mutations were constructed in the **CH**3 domain of humanized anti-CD3 Ab **H** chain and in the CD4-IgG, and the CH3/CH3 interface involves 16 residues on each domain. In contrast to chains containing the wild-type CH3, the hybrid was recovered in yields of up to 92% from co-transfections in which the anti-CD3 **H** chain and CD4-IgG contained the Y407T hole and T366Y knob mutations, respectively. Further because each of the Ab and the CD4-IgG of Ridgeway is expressed on a different phagemid within the same cell, there is no requirement that the proteins would necessarily be expressed at the same time absent a showing by Applicants to the contrary.

Ridgeway states: "This augurs well for the preparation of larger quantities of hybrids using stable cell lines where the relative expression levels of the Ab and CD4-IgG are less readily manipulated than in the transient expression system used here."

Ridgeway states: "The T366Y and Y407T mutations are directly applicable to the construction of bispecific IA, which further expand IA as a class of novel therapeutic. In addition the mutations identified are anticipated to increase the clinical potential of ***Fc-containing BsAb*** by reducing the complexity of the mixture of products obtained from a possible 10 major species down to four or less."

Rideway provides sufficient motivation to use the holes-to-knobs approach in a single cell system to create other antibody fragments such as the bispecific antibodies of the instant claims including the BsF(ab)2 of Shalaby. Shalaby provides methods for expressing a Fab' in a dicistronic format where both the light chain and heavy chain are under the transcriptional control of the phoA promoter. The general skills and technology to modify the expression unit of Ridgway according to the expression units of Shalaby for use in the method of Ridgeway would seemingly have been obvious at the time of the invention especially to produce a full length bispecific antibody within the same cell.

Rideway provides sufficient motivation to use the holes-to-knobs approach in a single cell system to create other antibody fragments such as the bispecific antibodies of Peipp. Peipp teaches "Recombinant bispecific antibodies can be successfully produced in various expression systems (see Table 2 for examples of expressing recombinant bispecific antibodies in CHO cells)"...and "While bacterial expression offers the potential for large yields, difficult refolding procedures may be required to obtain functional proteins. Today, production in Escherichia coli is most commonly used for the diabody format, while short-chain bispecific antibodies are preferentially expressed in mammalian cells. Interesting novel expression systems include yeast or insect cells, as well as transgenic plants or animals [38,39]. For production of clinical-grade material, however, these later systems are less well defined regarding potentially dangerous contaminants, and furthermore differ substantially from mammalian cells with respect to their glycosylation pattern."

Thus in order to produce abundant yield of heterodimeric, bispecific antibodies which are optimally expressed, dimerize with their corresponding complementary chain and are properly glycosylated, the ordinary artisan would have found more than sufficient motivation to have used the method of Ridgeway as a starting point for expressing heterodimeric antibodies in a single eukaryotic cell using a dicistronic vector or separate vectors encoding the light and heavy chain complementary pairs in order to ensure differentially timed expression for equimolar expression and dimerization of the complementary light and heavy chain in order to avoid mispairing followed by the further pairwise association of the different heavy chains through the knobs-to-holes variation.

Applicants' allegations on pp. 7-9 of the Response of 6/10/09 have been considered and are not found persuasive. Applicants allege that none of the references teach "anything about controlling the timing of expression of heavy and light chains within a cell" and "the use of four different chains: two light chains and two heavy chains"; and "the references teach that, in order to ensure proper pairing of heavy and light chains in a bispecific antibody context, one should either (a) express one pair in one set of cells and the other pair in a different set of cells, or (b) reconfigure them as recombinant diabodies or single-chain bispecific antibodies."

Response to Arguments

The examiner respectfully submits that the references are not so limited as to the possibility of resultant antibodies that could be generated from combining their disclosed techniques. For example, and as stated in the Office Action of 9/11/08, Shalaby provides methods for expressing a Fab' in a dicistronic format where both the light chain and heavy chain are under the transcriptional control of the phoA promoter. The general skills and technology to modify the expression unit of Ridgway according to the expression units of Peipp and Shalaby for use in the method of Ridgeway would seemingly have been obvious at the time of the invention especially to produce a full length bispecific antibody within the same cell. For example Peipp provides in Figure 1 (3rd example, top row), "Schematic representation of the most common bispecific antibody formats" and specifically shows an example of a knobs-into-holes antibody comprising two different light chains and two different heavy chains where the heavy

chains are linked by the knobs-into-holes feature engineered into the constant region of the heavy chain. Finally, as stated in the Office Action of 9/11/08, Ridgeway states on p. 620, Col. 2, ¶4: "The T366Y and Y407T mutations are directly applicable to the construction of bispecific IA, which further expand IA as a class of novel therapeutic. In addition the mutations identified are anticipated to increase the clinical potential of Fc-containing BsAb by reducing the complexity of the mixture of products obtained from a possible 10 major species down to four or less. The T366Y and Y407T mutant pair will likely be useful for heterodimerization of other human IgG isotypes since T366 and Y407 are fully conserved and other residues at the CH3 domain interface of IgG1 are highly conserved." Ridgeway specifically contemplates that the knobs-to-holes technique could be expanded to include other full length IgG molecules. Further and as evidenced by the references alone or in combination and the general state of art at the time of the invention, cloning the two different heavy chain and two different light chains to read on the vector constructs of Claims 24-26 would have been well within the skill of the ordinary artisan for recombinant antibody technology. (MPEP 2141; *KSR* stating a rationale for obviousness includes an "obvious to try" where the ordinary artisan would choose from a finite number of identified, predictable solutions, with a reasonable expectation of success"). Here both Ridgeway and Shalaby were successful in using different techniques to co-express two light chain and two heavy chains and thus to have combined the techniques further in view of Piepp who illustrated the resultant claimed antibody product with knoeb-to-holes would have been prima facie obvious at the time of the invention. Additionally, that the ordinary artisan would use an expression-

inducible promoter such as tetracycline was well known in molecule biology and availabel to the ordinary artisan.

The obviosness of using knobs-to-holes is admitted by Applicants' own attorney statements of record, where on p. 11 of the Response of 6/10/09, they state:

That this technique is well known in the art is illustrated by the fact that at least three publications of record (Ridgway, Peipp and the previously-cited Carter, J. Immunol. Methods 248:7-15, 2001) describe its use in production of bispecific antibodies. Knowledge of the technique thus goes back to at least 1996."

The rejection is maintained.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Enablement***

9. The rejection of Claims 1, 6, 8 and 22 (and new Claims 23, 27 and 28) under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for inducing just any kind of cell to express a first light chain and a first heavy chain at one time and to express a second light chain and a second heavy chain at a different time under just any conditions.

New claims 23, 27 and 28 are joined under this rejection because they are not considered as being any more enabling for a cell type directed towards co-expressing the different antibody chains within the same cell.

For purposes of review, the rejection was set forth in the Office Action of 9/11/08 as follows:

"Nature of the Invention/ Skill in the Art

Claims 1, 6, 8 and 22 are interpreted as being drawn to a method for producing an antibody in a cell comprising expressing a first light and heavy chain at one time and expressing a second light and heavy chain at a different time and where the light chains are different and the heavy chains are different (Claim 1), where the antibody is bispecific and the first light and heavy chain recognize one antigen and the second light and heavy chain recognize a second antigen (Claim 6), where the antibody is prepared by using the knobs-into-holes technique (Claim 8), and where the first light and heavy chain expression is under the control of a first expression regulator and the second light and heavy chain expression is under the control of a second expression regulator and each of the expression regulators are different, where (i) the first light and heavy chain and second light and heavy chain are encoded by the same vector or (ii) the first light and heavy chain are encoded by a first vector and the second light and heavy chain are encoded by a second vector (Claim 22).

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure of the Specification

Specific examples of methods for expressing the first and second pairs of antibodies at different times include methods that induce the expression of the first and second pairs of antibodies at different times using expression regulators. More specifically, a vector in which expression of a first pair can be induced by a first expression regulator, and a vector in which expression of a second pair is inducible by a second expression regulator, are constructed. The first pair and second pair may be constructed in a single vector, or two or more different vectors. Alternatively, the H chain and L chain may be constructed in a single vector, or two or more different vectors. Next, the obtained vector constructs are introduced into cells, and expression of the first pair is induced by the first expression regulator, and then expression of the second pair is induced by the second expression regulator. In this case, expression of the first pair is preferably turned off before expression of the second pair is induced [0056].

A specific example of the methods for producing antibodies of the present invention is described where "First, the H and L chains on the left arm of an antibody (Left HL) and the H and L chains on the right arm of the antibody (Right HL) are respectively cloned into a tetracycline inducible pcDNA4 vector (Invitrogen) and an ecdysone inducible pIND vector (Invitrogen). All of the expression-regulated plasmids are introduced into the above-mentioned suitable host cells, for example, animal cells such as COS-7 cells. For example, for the first induction tetracycline is added to the medium, and a Left HL molecule is formed in the cells. One to two days after the first induction, the medium is washed away to completely remove the first agent (tetracycline, in this case). Next, the cells are placed in a fresh medium containing an ecdysone analogue, the agent for the second induction, and the second induction is conducted for two to three days. Consequently, a Right HL molecule is produced and associates with the Left HL molecule already present in the cells, thus forming a complete BsAb form, which is then secreted into the medium" [0065].

The expression regulators are not particularly limited, and any kinds of expression regulators may be used as long as they can regulate expression of H chains and L chains in host cells. For example, expression may be induced in the presence of an expression regulator, and not in its absence; or conversely, expression may be induced in the presence of an expression regulator, and not in its absence. Expression regulators may be chemical compounds such as expression inducing agents, or physical factors such as temperature (heat). Specific examples of expression inducing agents include antibiotics such as tetracycline, hormones such as ecdysone analogues, and enzymes such as Cre (a homologous recombination enzyme which causes recombination). In addition, induced expression of an H chain and/or L chain may be halted by removing the expression inducing agent that functions as an above-mentioned expression regulator. If a physical factor such as temperature (heat) is used as an expression regulator, the induced expression of an H chain and/or L chain can be halted by returning to a temperature that does not permit induction of expression [0057].

Claim 22, element (i) is drawn to expressing both antibody pairs from the same vector, and the specification provides a single statement for expressing both antibody pairs from the same vector. No examples of a poly-cistronic expression vector are taught or disclosed, and no references citing examples of a poly-cistronic expression vector are cited which meet all the required claim limitations.

A method using any cell with the properties of the instant claims is unpredictable and requires undue experimentation.

In order to obtain a bispecific antibody comprising the heavy and light chain constant domains and using the knobs-to-holes technique required by the instant method, and in order to produce abundant yield of heterodimeric, bispecific antibodies which are optimally expressed and dimerize with their corresponding complementary chain and are properly glycosylated, the ordinary artisan could not have used just any wild-type cell as instantly claimed. This is

because according to Peipp (Biochem. Soc. Trans. 30:507-511 (2002); cited in the IDS of 4/28/06) "Recombinant bispecific antibodies can be successfully produced in various expression systems (see Table 2 for examples of expressing recombinant bispecific antibodies in CHO cells)"...and "While bacterial expression offers the potential for large yields, difficult refolding procedures may be required to obtain functional proteins. Today, production in Escherichia coli is most commonly used for the diabody format, while short-chain bispecific antibodies are preferentially expressed in mammalian cells. Interesting novel expression systems include yeast or insect cells, as well as transgenic plants or animals [38,39]. For production of clinical-grade material, however, these later systems are less well defined regarding potentially dangerous contaminants, and furthermore differ substantially from mammalian cells with respect to their glycosylation pattern." Further, Ridgeway et al., (Protein Eng. 9:617-612 (1996); cited in the IDS of 4/28/06) teach the successful use of an in vitro eukaryotic cell system to express an Ab/CD4-IgG using the knobs-to-holes technique which is taught as being adaptable to creating bispecific antibodies.

The specification does not nearly suggest that the ordinary artisan could remotely practice the invention using any cell and in the absence any particular reagents as is otherwise required by the instant claims. The ordinary artisan would be required to practice undue trial and error experimentation just to identify any wild-type cell having the ability to differentially express a first light and heavy chain much less a second light and heavy chain within the same cell, and further wherein the antibody is generated using a knobs-into-holes technique when the instant claims which do not specify where within the antibody structure, the knobs-to-holes mutation should be introduced. Thus Applicants have not identified a naturally occurring cell that can be induced under any conditions to express two different antibodies (or antibodies against different antigens) within or by the same cell.

Similarly, the ordinary artisan would be required to perform undue trial and error experimentation to test various different compounds for expression regulating effects on the endogenous promoters for the first light and heavy chain, and different compounds for expression regulating effects on the endogenous promoters for the second light and heavy chain, especially where the compound-inducible expression regulation is required to be performed in the same cell in order for the same wild-type cell to differentially express the different light/heavy chain pairs.

The ordinary artisan would be required to practice undue trial and error experimentation in order to construct a poly-cistronic vector enabled to express in a different time frame the first antibody pair and then the second antibody pair and all occurring within the same cell, because no guidance is provided in the original specification as filed for the starting materials and/or the generation of any such vector construct.

Applicants could overcome the rejection by introducing amendments into the method claims more particularly describing those steps and reagents which are required to practice the method as supported and enabled by the original disclosure."

Applicants' allegations on pp. 10-12 have been considered and are not found persuasive. Applicants allege "one of ordinary skill in the art would presumably seek a simple route to the final result: e.g., transfecting the cell with recombinant nucleic acid encoding the four polypeptides, with expression of the mRNAs encoding the polypeptides driven by known inducible promoters" and that the instant claims read on such elements. For example, "In the methods of the invention, the four polypeptides could be encoded on two separate bicistronic vectors, as illustrated in Example 1 of the specification. Alternatively, the four polypeptides could be encoded on four separate vectors (one coding sequence per vector) or on three vectors (two coding sequences on one, and one coding sequence on each of the other two), or all on a single vector. (The

vectors could, of course, be integrated into the cell's genome to produce a stably transfected cell.)"; and "That this technique *[knobs-into-holes; examiner's italics]* is well known in the art is illustrated by the fact that at least three publications of record (Ridgway, Peipp and the previously-cited Carter, J. Immunol. Methods 248:7-15, 2001) describe its use in production of bispecific antibodies. Knowledge of the technique thus goes back to at least 1996."

Response to Arguments

The examiner respectfully submits that the amendment of the claims to read on a eukaryotic cell does not obviate the original grounds for rejection, which is that Applicants have yet to demonstrate a working example of a wild-type eukaryotic cell capable of being used in the invention method to co-express two light chains and two heavy chains where the heavy chains are paired via knobs-to-holes. Thus absent Applicants submission of evidence showing any such cell exists much that it is capable of undergoing these steps or amending the generic claims 1 and 28 to indicate that the eukaryotic cell is *recombinant and vector transformed*, the skilled artisan could not conceivably practice the invention without further and undue experimentation. This rejection is maintained because the claims fail to meet the how-to-use aspect of the enablement requirement.

## ***New Grounds for Rejection***

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 1, 6, 8, 22, 23, 27 and 28 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility.

Generic claims 1 and 28 are interpreted as being drawn to a non-operative invention, namely, a eukaryotic host cell comprising DNA encoding a first light and heavy chain and DNA encoding a second light and heavy chain; and DNA encoding a second light and second heavy chain, where the eukaryotic host cell can effectively express two different antibodies comprising the first light and heavy chain and the second light and heavy chain (Claim 1); or a eukaryotic host cell containing (i) nucleic acid encoding a first light chain and nucleic acid encoding a first heavy chain that bind to a first antigen, and (ii) nucleic acid encoding a second light chain and nucleic acid encoding a second heavy chain that bind to a second antigen, wherein the amino acid sequences of the heavy and light chains differ, the heavy chains comprise one or more mutations, where the eukaryotic host cell can effectively express two different antibodies comprising the first light and heavy chain and the second light and heavy chain (Claim 28).

Applicants specification and the prior art does not recognize any single eukaryotic host cell that can rearrange its genome for an antibody gene much less to express a first light and first heavy chain under certain inducible conditions, and then be further induced to rearrange its genome a second time to express a second light and a second heavy chain. Applicants' claims are describing an element of the invention, namely, the eukaryotic host cell, which is not defined in the field of art and is not

recognized as being capable of undergoing these steps, thus rendering the element of Claims 1 and 28 inoperative.

The role of site-specific recombination in the formation of immunoglobulin genes was first demonstrated by Susumu Tonegawa in 1976 (Hozumi, N. & Tonegawa, S. Proc. Natl. Acad. Sci. U.S.A. 73, 3628–3632 (1976)). Although every individual is capable of producing a vast spectrum of different antibodies, *each B lymphocyte produces only a single type of antibody*. Tonegawa's key discovery was that each antibody is encoded by unique genes formed by site-specific recombination during B lymphocyte development. These gene rearrangements create different immunoglobulin genes in different individual B lymphocytes, but there has been no demonstration of an individual B cell or any eukaryotic cells undergoing site-specific recombination for two different antibodies within the same cell. (MPEP 2107.01 states in part: An invention that is "inoperative" (i.e., it does not operate to produce the results claimed by the patent applicant) is not a "useful" invention in the meaning of the patent law. See, e.g., Newman v. Quigg, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989); In re Harwood, 390 F.2d 985, 989, 156 USPQ 673, 676 (CCPA 1968) ("An inoperative invention, of course, does not satisfy the requirement of 35 U.S.C. 101 that an invention be useful."). However, as the Federal Circuit has stated, "[t]o violate [35 U.S.C.] 101 the claimed device must be totally incapable of achieving a useful result." Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571, 24 USPQ2d 1401, 1412 (Fed. Cir. 1992) (emphasis added). See also E.I. du Pont De Nemours and Co. v. Berkley and Co., 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980) ("A small degree

of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . .).

***Conclusion***

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority